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Acute Phase Proteins as Biomarkers in Animal Health and Welfare

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1. Introduction

The acute phase proteins (APPs) are reactants synthesized during an acute phase response (APR) against several stimuli like infection, inflammation, stress, trauma or tissue damage (Petersen et al., 2004; Cerón et al., 2005). The main role of the APR is to restore the normal homeostasis of the organism after any of the stimuli mentioned above. In this sense, the APR is considered as part of the innate immune system triggering off functions just as leukocytosis, fever, chelation of serum zinc and iron, or opsonization (Cerón et al., 2005). During the APR organic concentrations of APPs may change, and measuring APPs levels is being used widely nowadays both in human and in veterinary medicine. The concentration of APPs may increase or decrease after an appropriate stimulus being classified as positive, moderate or negative APPs depending on the enhancement of its concentration. Thus, a positive APP may show up to 100-1000-fold increase in its serum concentration in 1-2 days; a moderate APP displays a 5 to 10-fold increase in 2-3 days; and a minor APP increase between 50% and 100%. Negative APPs are those which decrease after a specific stimulus (Petersen et al., 2004; Cray et al., 2009; Eckersall & Bell, 2010).

Serum samples are the most common sample used to measure the levels of APPs in both companion and farm animals. Recently, other specimens such as saliva or meat juice has been successfully used as samples for APPs measurements in dog (Parra et al., 2005) and pig (Gutiérrez et al., 2008; 2009). Saliva presents the advantage of being a non-invasive, easier and less stressful sampling method for the animals and meat juice represent a suitable alternative to serum or blood samples and simplifies the process of sampling collection at slaughter.

In this sense, the extrahepatic synthesis of APPs is one of the recent subjects of study in the field of the APR. The synthesis of APPs is regulated by both endogenous glucocorticoids and the production of proinflammatory cytokines, mainly interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α), which activate specific cells to synthesize APPs. The liver is the main target for the production of APPs, specially the hepatocytes; however, several extrahepatic sites have been reported. An extrahepatic synthesis of haptoglobin (Hp) has been reported in airway epithelial cells and immigrated leucocytes (Hiss et al., 2008) and extrahepatic production of C-reactive protein (CRP) has been observed in vascular smooth muscle cells (Kuji et al., 2007), pulmonary fibroblast and endothelial cells in the lung (Päiväniemi et al., 2009). In our group an extrahepatic expression of both Hp (Gutiérrez et al., 2011) and CRP (unpublished data) has been observed in epithelial cells from the respiratory tract, in the parotid salivary gland and in diaphragmatic myofibers from sick pigs (Fig. 1).

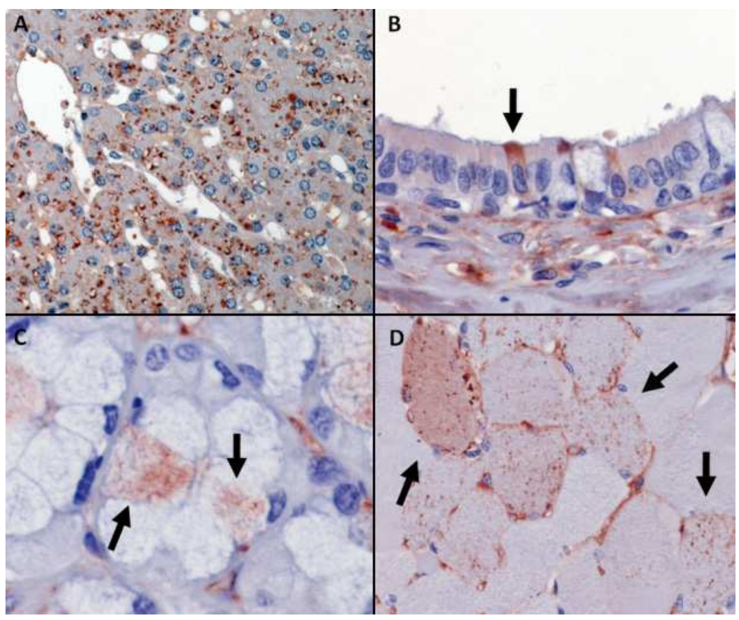

Fig. 1. Immunohistochemical haptoglobin expression in hepatocytes (1A), airway epithelial cells (1B, arrow), epithelial glandular cells (1C, arrows), and diaphragmatic myofibers (1C, arrows).

Before describing the role of APPs in veterinary medicine, it should be useful to remind some of the functions of the main APPs. The main biological function of Hp consists on prevention of iron loss by the formation of haemoglobin-iron complexes (Ceciliani et al., 2002; Petersen et al., 2004). Therefore, Hp develops a bacteriostatic effect reducing the level of available iron for the microorganisms (Petersen et al., 2004). The expression of Hp has also been related to the secretion of anti-inflammatory cytokines, particularly IL-10, through the interaction with CD163, a haemoglobin scavenger receptor that is solely present in cells of monocyte/macrophage lineage (Moestrup & Moller, 2004; Philippidis et al., 2004). However, the exact mechanism used by Hp as modulator of the immune response is not clear, acting as suppressor of lymphocyte proliferation in bovine (Murata & Miyamoto, 1993), and as supporter of B and T lymphocytes proliferation and differentiation in Hp-deficient C57BL/6J mice (Huntoon et al., 2008).
Serum amyloid A (SAA) shows more than 100-fold increase after any injury, which triggers off the APR (Petersen et al., 2004). SAA carries out several functions related with the

inflammatory response, just as cholesterol removal from the local site of inflammation and transport to hepatocytes; chemotaxis of monocytes, polymorphonuclear leukocytes and T cells; inhibitory effect on fever, oxidative burst, platelet activation and in vitro immune response (Ceciliani et al., 2002; Petersen et al., 2004). Secondary amyloidosis is triggered by a conformational change of SAA into an insoluble peptide, AA, which takes place when there is a marked high expression of SAA (Ceciliani et al., 2002).

CRP was first discovered in the serum of patients which suffered a pneumococcal infection, as a substance which reacted with C polysaccharide (Petersen et al., 2004). In the acute phase response, CRP increases often more moderately than Hp or SAA, showing between 1 to 10 times increase (Petersen et al., 2004). Although some authors consider CRP as a useful tool to differentiate between a bacterial or a viral infection, other authors could not detect such differences because of the individual variability (Petersen et al., 2004). CRP participates in the innate immune response removing bacteria and damaged cells by complement activation and opsonisation, activating monocyte/macrophage to inflammatory cytokines production, and preventing neutrophils migration (Ceciliani et al., 2002; Petersen et al., 2004). Since CRP is a component of the innate response, it may be considered as an early bioindicator of health status in swine herds (Stevenson et al., 2006).

This chapter will deal with the role of APPs in domestic animal species, as well as their role in animal welfare, in disease and in the evaluation of prophylactic and therapeutic strategies.

2. Useful acute phase proteins in domestic animal species

As mentioned above, APPs are classified as positive, moderate, minor or negative depending on either the enhancement or the decrease in their serum concentration during the APR (Petersen et al., 2004; Cray et al., 2009; Eckersall & Bell, 2010). The synthesis and role of APPs may differ depending on the animal species. In this sense, whereas an APP may act as a positive APP in one species, it may not suffer any change in other species, such as CRP in swine and in cattle, respectively (Table 1).

Species	Major APP	Moderate APP	Minor APP	Negative APP
Dog	CRP, SAA	AGP, Hp, Cp, Fb	-	Albumin, Tf
Cat	AGP, SAA	Hp	-	Albumin, Tf
Horse	SAA	Hp, Fb	-	Albumin
Swine	Pig-MAP, Hp, SAA	AGP, CRP	Fb	Albumin, Apo A-I
Cattle	Hp, SAA	AGP, MAP	Fb	Albumin
Sheep	Hp, SAA	AGP	Fb, Cp	Albumin
Goat	Hp, SAA	Fb, ASG	Cp	Albumin

CRP: C-reactive protein; SAA: serum amyloid A; AGP: α_1-acid glycoprotein; Hp: haptoglobin; Cp: ceruloplasmin; Fb: fibrinogen; Tf: transferrin; Pig-MAP: pig major acute phase protein; Apo A-I: apoliprotein A-I; MAP: major acute phase protein; ASG: acid soluble glycoprotein.

Table 1. Expression of APPs in different species according to their degree of importance.

It is well established that albumin participates as a negative APP in most of the animal species. On the other hand, Hp and fibrinogen (Fb) are considered as positive APPs, although the enhancement shown by the former may be up to ten times higher than the one observed by the latter. CRP is a really useful biomarker in human for monitoring the course of different clinical processes, and its measure is also of interest in swine and dog. Nonetheless, the serum concentration of CRP does not suffer big changes in the APR in bovine or in cat. Therefore, the selection of the appropriate APP for each species is of key importance.

2.1 APPs of significance in small animals

The APR is mounted in a similar way both in dogs and cats; however they show few differences with respect to the behaviour of some APPs. Whereas Hp, SAA, and α_1-acid glycoprotein (AGP) are considered as positive APPs in both species, CRP acts as a positive APP in dogs but usually shows no changes in cats (Petersen et al., 2004; Cerón et al., 2005; Eckersall and Bell, 2010). In addition, Fb is a positive APP in dogs, but no information is available in cats (Petersen et al., 2004; Cerón et al., 2005). Finally, albumin participates as a negative APP in all mammalian species (Mackiewicz, 1997).

2.1.1 Canine APPs

In the dog the main APPs to consider are CRP and SAA, as positive APPs; AGP, Hp and ceruloplasmin (Cp), as moderate APPs; and albumin and transferrin, as negative APP (Petersen et al., 2004; Cerón et al., 2005) (Table 1). No age- or sex-related differences have been observed in the concentration of CRP for dogs (Yamamoto et al., 1994), however, adult dogs respond to inflammation with a higher enhancement in the concentration of both CRP and AGP than young animals do (Hayashi et al., 2001).

The concentration of APPs has been reported to rise after several bacterial, viral or parasitic infections, in autoimmune disorders and in neoplasia (just as lymphoma) (Table 2). In this sense, the magnitude of the increase of different APPs has been reported as a valuable tool to monitor parvoviral (Kocaturk et al., 2010) and *Erlichia canis* (Rikihisa et al., 1994) infections. Moreover, a correlation has been observed between the levels of APPs and the remission of the autoimmune hemolytic anemia (Mitchell et al., 2009). Some studies have been focused on the role of APPs in the monitoring of mammary tumors in the bitch but the results are contradictory. In these reports, the changes observed in the concentration of APPs have been related mainly to the inflammation associated to the tumor (Planellas et al., 2009; Tecles et al., 2009).

In the same way, it is interesting to take into account that the measure of APPs may not be of help in several processes. Nakamura et al. (2008) performed a study to determine the role of CRP in different diseases, concluding that the measure of CRP was not useful in neurological and endocrine processes.

2.1.2 Feline APPs

The APR has not been thoroughly studied in cats. However some relevant data are available in the literature. AGP and SAA act as positive APPs in the APR in cats, whereas Hp participates as a moderate APP and albumin and transferring as negative APPs (Petersen et al., 2004; Cerón et al., 2005; Paltrinieri, 2008) (Table 1). No age-related differences have been observed in the concentration of APPs in cats (Campbell et al., 2004).

Although scarce studies have been carried out to determine the role of APPs in feline species, there are several studies available concerning the role of APPs in feline infectious peritonitis (FIP) (Table 3). Thus, a persistent increase in the concentration of AGP, SAA and Hp has been reported in cats suffering from FIP (Giordano et al., 2004; Paltrinieri et al.,

Disorder		Acute Phase Protein	Reference
Inflammation	Acute pancreatitis	CRP	Nakamura et al., 2008
	Pyometra	CRP, Hp, SAA	Dabrowski et al., 2009
	Polyarthritis	CRP	Tvarijonaviciute et al., 2011
	Inflammatory bowel disease	CRP	Jergens at al., 2003
	Rhinitis	CRP, Hp	Sheahan et al., 2010
	Surgery	CRP , Hp, Cp	Serin & Ulutas, 2010
Bacteria	*Bordetella bronchiseptica*	CRP	Yamamoto et al., 1994
	Escherichia coli	CRP, SAA, Hp	Dabrowski et al., 2009
	Staphylococcus aureus	CRP, SAA, Hp	Dabrowski et al., 2009
	Leptospira interrogans	CRP, Hp	Mastrorilli et al., 2007
Viruses	Parvovirus	CRP, SAA, AGP	Yule et al., 1997 Kocaturk et al., 2010
Parasites	Babesiosis	CRP, SAA, AGP	Lobetti et al., 2000; Matjako et al., 2007
	Erlichia canis	CRP, AGP	Rikihisa et al., 1994
	Leishmania infantum	CRP, Hp, Cp	Martínez-Subiela et al., 2002
	Trypanosomiasis	CRP, Hp	Ndung'u et al., 1991
	Granulocytic anaplasmosis	CRP	Pantchev, 2010
Neoplasia	Round cell tumor (lymphoma) Carcinoma Sarcoma	CRP, AGP	Ogilvie et al., 1993 Mischke et al., 2007 Nakamura et al., 2008 Yuki et al., 2011
Endocrine	Cushing's syndrome	Hp, Fb	Caldin et al., 2009
Autoimmune	Autoimmune hemolytic anemia	CRP	Caspi et al., 1987
	Rheumatoid arthritis	Cp	Tecles et al., 2005

CRP: C-reactive protein; Hp: haptoglobin; SAA: serum amyloid A; CP: ceruloplasmin; AGP: α_1-acid glycoprotein.

Table 2. Main canine disorders and specific APPs that play a significant role in each disease (modified from Cerón et al., 2005).

2007b). Moreover, AGP has been shown to be useful in monitoring the early interferon (IFN) treatment of parvoviral infected cats (Paltrinieri et al., 2007a). SAA has been reported as a useful tool in the diagnosis, monitoring and treatment of feline pancreatitis (Tamamoto et al., 2009). An enhancement in the concentration of AGP and Hp has been observed in anemic cats suffering from pyothorax, abscesses or fat necrosis (Ottenjann et al., 2006). Some studies have been focused on the expression of APPs in cats with neoplasia, however, whereas some authors describe no changes in APPs concentration in cats with lymphoma (Correa et al., 2001) others show a significant increase of AGP or SAA in cats bearing carcinomas, sarcomas or round cell tumors (Selting et al., 2000; Tamamoto et al., 2008).

Disorder		Acute Phase Protein	Reference
Inflammation	Pancreatitis	SAA	Tamamoto et al., 2008, 2009
	Reactive amyloidosis	AGP, SAA, Hp	Kajikawa et al., 1999
	Renal failure, FLUTD[1]	SAA	Sasaki et al., 2003
	Abscesses, pyothorax, fat necrosis	AGP, Hp	Ottenjann et al., 1996
	Lipopolysaccharide	AGP, SAA, Hp	Kajikawa et al., 1999
	Injury, liver disorders	SAA	Sasaki et al., 2003
	Surgery	AGP, SAA, Hp	Kajikawa et al., 1999
Bacteria	*Chlamydophila psittaci*	AGP	Terwee et al., 1998
Viruses	Feline infectious peritonitis	AGP, SAA, Hp	Duthie et al., 1997 Giordano et al., 2004 Paltrinieri et al., 2007b
	Feline immunodeficiency	AGP, Hp	Duthie et al., 1997
	Parvovirosis	AGP	Paltrinieri et al., 2007a
	Feline calicivirus	AGP	Terwee et al., 1997
Neoplasia	Lymphoma Malignant mesothelioma Carcinoma Sarcoma	SAA, AGP	Selting et al., 2000 Sasaki et al., 2003 Tamamoto et al., 2008
Endocrine	Hyperthyroidism Diabetes mellitus	SAA	Sasaki et al., 2003 Tamamoto et al., 2008
Autoimmune	Autoimmune hemolytic anemia	SAA	Paltrinieri, 2007
	Polycystic disease Familial amyloidosis		Tamamoto et al., 2008

[1] FLUTD: Feline Low Urinary Tract Disease; SAA: serum amyloid A; AGP: α_1-acid glycoprotein; Hp: haptoglobin.

Table 3. Main APPs related with the diagnosis of feline disorders.

2.2 APPs of significance in large animals

In large animals, besides all the research carry out concerning the role of APPs in inflammatory and infectious disease, there is an intense ongoing investigation on the APR triggered off by the stress related to several conditions, such as transport, feeding or housing conditions. These studies are valuable in order to determine the animal welfare status of the herds in order to both improve the production and obtain products of higher quality.

2.2.1 Equine APPs

As in cats, there are just few studies concerning the role of APPs in horses. SAA is the main APP in equines participating in the APR as a major APP, whereas both Hp and Fb acts as moderate APPs. Similar to other mammalian species, albumin is considered as a negative APP (Cray et al., 2009; Eckersall & Bell, 2010) (Table 1). Attention must be paid to the age were the concentration of APPs is going to be measured. Thus, in the first week of life of the foal there is a physiological enhancement in the level of SAA, as well as in the mare just after foaling (Nunokawa et al., 1993; Paltrinieri et al., 1998). In addition, an increase of SAA is observed after vaccination (Andersen et al., 2011).

	Disorder	Acute Phase Protein	Reference
Inflammation	Surgery	SAA, Fb	Jacobsen et al., 2009
	Colic	SAA	Vandenplas et al., 2005
	Non-infectious arthritis	SAA, Hp, Fb	Hultén et al., 2002
	Infectious arthritis	SAA	Jacobsen et al., 2006a; 2006b
	Laminitis	Hp	Petersen et al., 2004
	Equine dysautonomia	Hp, Cp	Milne et al., 1991
Bacteria	*Escherichia coli* (endometritis)	SAA, Fb	Mette et al., 2010
	Streptococcus zooepidemicus (bronchopneumonia)	SAA	Hobo et al., 2007
	Septicemia	SAA	Paltrinieri et al., 2008
Viruses	Equine Influenza	SAA	Hultén et al., 1999
Stress	Training	Fb, Hp	Fazio et al., 2010
Others	Early embrionary death	SAA, Hp	Krakowski et al., 2011
	Vaccination	SAA, Fb	Andersen et al., 2011

AGP: α_1-acid glycoprotein; SAA: serum amyloid A; Hp: haptoglobin.

Table 4. Equine disorders and specific APPs for their diagnosis and monitoring.

Changes in the concentration of SAA have been reported in horses in several conditions, just as non-septic arthritis, laminitis, colic, or influenza infection. Other conditions which may lead to an increase in the level of this and/or another APPs in horses are shown in Table 4.

However, there are several conditions in which the use of APPs is not completely justified. In foals it is controversial if the measure of SAA may be a useful tool for the diagnosis of bronchopneumonia associated to *Rhodococcus equi* (Hultén & Demmers, 2002; Cohen et al., 2005). In addition, other plasmatic proteins, such as the plasma iron, have been reported to better reflect acute inflammation than do APPs (Borges et al., 2007). On the other hand, the levels of APPs are not affected by selenium dose or source (Calamari et al., 2010).

2.2.2 Bovine APPs

In bovines it is important to take into consideration that some APPs, just as CRP, are not useful tools to measure the APR. The major APPs in cattle are Hp and SAA, acting both AGP and major acute phase protein (MAP) as moderate APPs and Fb as a minor APP. Albumin participates in the APR as a negative responder (Petersen et al., 2004; Eckersall & Bell, 2010) (Table 1).

There are several factors that may imply variations in the expression of APPs. In this sense, the breed of the animals has to be considered before carrying out an analysis since, for example, the Holsteins show a prolonged production of the AGP, which is only slightly elevated in the Sahiwals (Glass & Jensen, 2007). In another study, differences with respect to the level of Cp in both calves and cows were observed between Angus and Romosinuano breeds in response to weaning and transportation (Qiu et al., 2007). Another factor to consider is the age of the animals, being increased the levels of the APPs at calving and reaching baseline values during the first 3 weeks of life (Orro et al., 2008).

Disorder		Acute Phase Protein	Reference
Inflammation	Lameness	Hp, SAA	Kujala et al., 2010; Smith et al., 2010
	Postpartum	Hp, SAA	Gabler et al., 2010; Humbledt et al., 2006
			Tóthová et al., 2010
	Chronic respiratory disease	Hp, SAA	Huzzey et al., 2009; Chan et
	Metritis	Hp, SAA	al., 2010
			Carroll et al., 2009
			Tabrizi et al., 2008
	LPS	Hp, SAA	Safi et al., 2008; Tabrizi et al.,
	Clinical mastitis	Fb, Cp	2008
	Subclinical mastitis	MAA, MHp, Fb	Nazifi et al., 2009a
	Traumatic reticuloperitonitis	SAA, Hp	
Bacteria	*Escherichia coli* (mastitis)	SAA, Hp, LBP*	Suojala et al., 2008
	Staphylococcus aureus (subclinial mastitis)	SAA, HP*	Eckersall et al., 2006
	Mannheimia haemolytica	SAA, Hp, Fb	Gånheim et al., 2003
	Pasteurella multocida	SAA, Hp, AGP	Dowling et al., 2004
Viruses	Bovine viral diarrhea virus	SAA, Hp, Fb	Gånheim et al., 2003
	BRSV[1]	SAA, Hp	Heegard et al., 2000
	Foot and mouth disease virus	Hp	Höfner et al., 1994
Parasites	*Trypanosoma congolense*	SAA	Meade et al., 2009
	Theileria annulata	SAA, Hp, Cp, Fb	Nazifi et al., 2009b
Stress	Weaning	Hp, Fb	Lynch et al., 2010
	Housing	Hp	Lynch et al., 2010
	Feeding (ruminal acidosis)	SAA, Hp, LBP	Khafipour et al., 2009
	Transport	SAA, Hp	Lomborg et al., 2008
Other	Fatty liver (F.l.)	Hp	Katoh & Nakagawa, 1999
	F.l. + abomasal displacement	Hp, SAA	Guzelbektes et al., 2010

[1]BRSV: bovine respiratory syncytial virus; *All the three APPs increased both in milk and serum. Hp: haptoglobin; SAA: serum amyloid A; Cp: ceruloplasmin; Fb: fibrinogen; MAA: milk A amyloid; MHp: milk haptoglobin; LBP: lipopolysaccharide-binding protein; AGP: α_1-acid glycoprotein.

Table 5. Main APPs reported in different disorders in cattle useful for their diagnosis and/or monitoring.

Several studies are available concerning the role of APPs in different disorders affecting bovine species (Table 5). Many of them are focused on the APR in mastitis, being interesting the higher concentration of Hp and LBP response triggered off in mastitis caused by gram negative bacteria than in those caused by gram positive bacteria (Wen et al., 2010). Some of these studies determine the differences between the concentration of APPs in serum and in

milk. As it could be expected in cases of mastitis, the concentration of APPs is much higher in milk than in serum (Tabrizi et al., 2008; Safi et al., 2009).
Other studies are also focused on the changes experimented by APPs against different stressors or metabolic conditions, such as hepatic lipidosis (fatty liver) (Table 5).

2.2.3 APPs in small ruminants

The APR in small ruminants is poorly described. The different APPs may play a similar role both in sheep and goat but some differences have been reported. Hp and SAA are considered as major APPs and Cp as a minor APP in both ovine and caprine APRs. Nonetheless, Fb participates as a minor APP in sheep but as a moderate APP in goat. AGP and acid soluble glycoprotein (ASG) are also moderate APPs of the ovine and caprine APRs, respectively (Table 1). In both species the concentration of albumin diminishes after an appropriate stimulus (González et al., 2008; Cray et al., 2009).
Most of the studies performed on sheep are focused on the role of APPs after several inflammatory stimuli, being carried out few studies concerning specific bacterial, viral or parasitic infections (Table 6). Some studies are focused on the expression of APPs against lentiviral infections, being observed a local expression of SAA (Sack & Zink, 1992) but no serum enhancement of Hp or Fb concentrations (de la Concha et al., 2000).
Few studies have been focused on the changes of APPs in milk secretions of sheep. Whereas SAA levels in milk may be useful for the diagnosis on subclinical mastitis in individual ewes further studies are needed to determine its usefulness from bulk milk (Winter et al., 2006). Interestingly, opposite to bovine, the changes in the concentration of SAA in ewes with mastitis experimentally induced by *Staphylococcus epidermidis* are observed earlier in serum than in milk (Winter et al., 2003).
In goats the studies are rather limited than in sheep. The measure of APPs has been shown to not imply any advantage against the traditional markers observed for the diagnosis of pregnancy toxemia (González et al., 2011). Moreover, an increase of several APPs has been observed in the Alpine ibex with sarcoptic mange (Rahmann et al., 2010), which probably would act in the same way in domestic goats.

2.2.4 Porcine APPs

In swine there is an extensive literature available concerning the usefulness of APPs as a tool for monitoring both the health status of a herd as well as its welfare conditions. In pigs there are three major APPs, namely Hp, SAA and pig-major acute phase protein (Pig-MAP), whereas CRP and AGP are considered as moderate APPs and Fb as a minor APP (Petersen et al., 2004; Cray et al., 2009). Gender differences have been reported in swine exposed to stressors, being observed significantly higher concentrations of CRP and Hp in females than in males, although males tend to have higher Pig-MAP concentrations (Piñeiro M et al., 2007).
As it has just been said, APPs have been tested in pigs after exposure to stress (Salamano et al., 2008) and after natural (Chen et al., 2003; Parra et al., 2006) or experimental infections (Francisco et al., 1996; Asai et al., 1999; Magnusson et al., 1999; Knura-Deszczk et al., 2002; Van Gucht et al., 2005; Stevenson et al., 2006). Increased levels of different APPs have been reported in porcine viral and bacterial infections. The most significant of them are summarized in Table 7. As occurred in other species, inflammation or bacterial diseases trend to trigger off a more marked APR with a higher increase in the concentration of APPs

	Disorders in ovine	Acute Phase Protein	Reference
Inflammation	Peptidoglycan-polysaccharide	Hp, SAA	Dow et al ., 2010
	Uterine involution	Hp	Regassa & Noakes, 1999
	Pneumonia	Hp, Cp, Fb	Pfeffer & Rogers, 1989
	Chronic pneumonia	SAA	Kingston et al., 1982
	Subclinical mastitis	SAA	Winter et al., 2006
	Intrathoratic yeast inyection	Hp, Cp, Fb	Pfeffer et al., 1993
	Surgery	Hp, Cp, Fb	Pfeffer & Rogers, 1989
	Castration	Hp	Paull et al., 2009
Bacteria	*Corynebacterium pseudotuberculosis*	Hp, SAA, AGP	Pépin et al., 1991; Eckersall et al., 2007
	Mannheimia haemolytica	Hp, SAA, CRP, Cp	Ulutas & Ozpinar, 2006
	Staphylococcus epidermidis (mastitis)	SAA	Winter et al., 2003
Viruses	Lentivirus	SAA	Sack & Zink, 1992
Parasites	Myasis	SAA, Hp, Fb	Colditz et al., 2001; O'meara et al., 1995
Stress	Feeding	SAA	Eckersall et al., 2008
Other	Mulesing	Hp, SAA, Fb	Lepherd et al., 2011
	Carprofen + mulesing	Hp	Colditz et al., 2009
	NSAIDs + mulesing	Hp	Paull et al., 2008
	Vaccination	Hp, SAA	Eckersall et al., 2008
	Disorders in goats	**Acute Phase Protein**	**Reference**
Inflammation	Pregnancy toxemia	Hp	González et al., 2011
	Turpentine oil	Hp, SAA, ASG, Fb	González et al., 2008
Viruses	Lentivirus	SAA	Sack & Zink, 1992
Parasites	*Sarcoptes scabiei*	SAA, AGP, Hp, Cp	Rahmann et al., 2010
	Trichuris spp. + *Trichostrongylidae* spp. + *Fasciola* spp.	SAA, Hp	Ulutaş et al., 2008

Hp: haptoglobin; SAA: serum amyloid A; Cp: ceruloplasmin; Fb: fibrinogen; AGP: α_1-acid glycoprotein; CRP: C-reactive protein; ASG: acid soluble glycoprotein.

Table 6. Main APPs reported in different disorders in small ruminants.

than viral infections, however, the infection with specific porcine viruses such as porcine circovirus type 2 induces an enhancement in APPs comparable to the one observed in inflammation or *Mycoplasma hyopneumoniae* infection (Parra et al., 2006).

Recently, an interesting paper regarding the role of APPs in the diagnosis of infectious diseases in pigs has been published. In this paper the authors demonstrate specific combinations of APPs which may help to the diagnosis of porcine infectious diseases better than the analysis of individual APPs (Heegard et al., 2011).

Disorder		Acute Phase Protein	Reference
Inflammation	Lipopolysaccharide		Dritz et al., 1996
	Surgery	CRP, Hp	Hernandez-Richter et al., 2001
Bacteria	*Actinobacillus pleuropneumoniae*	SAA, CRP	Skovgaard et al., 2009
	Mycoplasma hyopneumoniae	Pig-MAP, Hp, CRP	Parra et al., 2006
	Streptococcus suis	SAA, CRP	Sorensen et al., 2009
	Bordetella bornchiseptica +		Francisco et al., 1996
	Pasteurella multocida type D	Hp	Magnusson et al., 1999
	Mycoplasma hyorhinis	Hp	Jacobson et al., 2004
	Brachyspira hyodysenteriae	SAA, Hp	
Viruses	PRRS[1]	Pig-MAP, Hp	Gómez-Laguna et al., 2010a
	PCV2[2]	Pig-MAP, Hp	Grau-Roma et al., 2009
	Influenza	Hp, CRP	Barbé et al., 2011
	Aujeszky	Hp	Parra et al., 2006
Parasites	*Toxoplasma gondii*	Hp	Jungersen et al., 1999
Stress	Transportation	Pig-MAP, Hp	Piñeiro et al., 2007
	Housing	Hp, CRP	Salamano et al., 2008
	Slaughter	SAA, CRP, Pig-MAP, Hp	Piñeiro M et al., 2007
Others	Gestation	Fb	Sorrels et al., 2007

[1]PRRS: porcine reproductive and respiratory síndrome; [2]PCV2: porcine circovirus type 2; CRP: C-reactive protein; Hp: haptoglobin; SAA: serum amyloid A; Pig-MAP: pig-major acute phase protein; Fb: fibrinogen.

Table 7. Main conditions and APPs increased in the early response in pigs.

Although several studies are being conducted to determine the welfare status of several potential stressors in pigs, just as transportation, housing conditions, feeding or slaughter, a lack of an evident APR is reported in some investigations (Johnson et al., 2008; Weber et al., 2008). In the Table 7 appear some conditions which may evoke an increase in APPs.

3. Acute phase proteins as biomarkers of animal welfare

Stress is considered to be the most important factor to control on animal welfare. Hans Selye was the first author to introduce the concept of stress in 1936, as the non-specific response of the body to external challenges such as pathogens or a harsh physical environment (Selye, 1998). Nowadays in the animal production systems some aspects related to the housing and feeding system, changes in diet and transportation are considered as causes of stress, which compromise the welfare of animals (Broom & Johnson, 1993). Also, stress causes a risk in the animal homeostasis which results in an inflammatory response leading to immunosupression. This immunosupression favors the appearance of diseases such as shipping fever of feedlot cattle and Glasser's disease in pigs. Additionally, poor welfare may conduct to losses in performance and meat quality. Recently, the population has a significant and increasing concern for animal welfare where consumers prefer to pay higher prices for those products whose quality is guaranteed.

Animal welfare can be measured by different parameters such us mortality in the herd, presence of injuries, behavioral assessment, plasma glucocorticoid concentrations and heart rate (Broom & Johnson, 1993). Nonetheless, a high number of measured factors should be done to establish a reliable evaluation (Grandin, 1997). Different studies have shown that APPs are a useful tool in the assessment of animal welfare (Eckersall, 2000; Murata et al., 2004). With the measure of APPs, a rapid diagnosis can be made before the behavioral signs appear, as a result an effective treatment can be performed in order to solve losses in performance.

Firstly, it is definitely important to know the baseline APPs concentrations in healthy animals just to establish the reference ranges for the proteins. Different studies (Heegaard et al., 1998; Petersen et al., 2002; Campbell et al., 2005; Carpintero et al., 2005; Martín et al., 2005; Clapperton et al., 2007; Piñeiro et al., 2007, 2009) have determined the baseline ranges of APPs in pigs, these results were summarized by Diack et al. (2011).

There is no agreement if the age of the animal can modify the baseline levels of APPs. Thus, Piñeiro C et al. (personal communication) pointed to not changes in APPs values, whereas Alsemgeest et al. (1993, 1995) and Orro et al. (2008) showed significant differences depending on the age in calves. Also, there were significant differences between genetic lines for CRP, Pig-MAP and transthyretin in pigs, the same finding was reported by Frank et al. (2005), Shutterland et al. (2006), and Clapperton et al. (2005, 2007). These results highlight that APPs concentrations should be adjusted for factors such as age, sex, genetic line or individual herds, being needed the determination of a reference range which allow a reliable use of APPs measurement. Even, it has been reported that the same stressor can cause differences among animals (Von Borell, 1995).

Recently, some authors have shown that it is more significant to study the correlation between two APPs than the changes of the level of only one APP following a stressful situation. In this sense, significant correlations have been found between Hp and CRP (Diack et al., 2011), between Hp and Pig-MAP (Clapperton et al., 2007; Diack et al., 2011) and between CRP and Pig-MAP (Diack et al., 2011) in pigs.

3.1 APPs and welfare in small animals

Dogs and cats also experience changes in their homeostasis due to stressors (Eckersall, 2000). Although it has not been reported any article about the behaviour of APPs in dogs and cats, cortisol levels have been reported to increase when dogs are introduced to novel kennels (Rooney et al., 2007) and where cats are maintained in non-enrichment shelter (McCobb et al., 2005). Knowing that APPs are sensitive biomarkers of welfare, it may be possible that an increase in APP concentration occurs after these conditions.

As a conclusion, not only transportation but also the stress of adapting to new environment comprising feeding, housing and different stock densities may cause an enhancement in APP concentration levels. Thus, the measure of APPs results in a useful parameter in order to assess animal's welfare, particularly in farm animals where the analysis of APPs could help to assess if the new automation machines are according to welfare conditions or in contrast are a cause of stress in animals and taking into account that a decrease in the APPs levels can express an adaptation to the stressful situation.

3.2 APPs and welfare in large animals

3.2.1 Bovine APPs of importance in stress and welfare

The majority of studies concerning to APPs performed in this species suffer from baseline ranges which allowed to compare the experimental results with the healthy situation.

Indeed, the absence of some control animals in the experiments carried out in matter of transportation and mixing animals, does not allow having a clear understanding of the APP behaviour. However, it is important to highlight that SAA suggests being the better APP to determine changes in weaning, feeding and housing systems in cattle.
Conner et al. (1988) described the increase of APPs in response to stress stimuli in calves. Table 8 summarized the studies performed in different possible stressful situations in this species.

Conditions	Acute Phase Proteins	Reference
3 hours transport after weaning	↑ SAA, Fb, Cp	Arthington et al., 2003
Road and sea transport	NC Hp, Fb	Earley & Murray, 2010
Mixing animals	NC Fb, Cp, AGP	Arthington et al., 2003
Dietary differences on diet	NC Hp, Fb, SAA	Berry et al., 2004
Different housing and feeding systems	↑ SAA NC Hp	Saco et al., 2008
Housing (different number of heifers per concentrate feeding place)	↑ Hp	González et al., 2008
Housing (different types of floor)	↑ SAA NC Hp	Alsemgeest et al., 1995
Parturition	↑ SAA, Hp, AGP, LPS	Orro et al., 2008

↑ : increased expression; NC: no change in expression; SAA: serum amyloid A; Fb: fibrinogen; Cp: ceruloplasmin; Hp: haptoglobin; AGP: α_1-acid glycoprotein; LPS: lipopolysaccharide.

Table 8. APPs levels depend on the studied stressor.

Regarding transportation, Arthington et al. (2003) showed changes in APPs levels, these changes were transient and not significantly altered. Also, the absence of a weaning control does not allow establishing a solid conclusion.
In cattle, it has been reported that competition for food can result in poor welfare and production losses (Miller & Wood-Gush, 1991). The results showed that the energy level of the diet does not induce changes in APP concentrations. The genetics background has also proven to be important in cows, where SAA levels showed an increase in semi-feral cows in comparison with feed type selected breed.
SAA was the main protein enhanced depending on the housing system, this major APP in cattle may be a better biomarker of the health status.
The results found in bibliography about parturition are controversial. Nonetheless, concentrations of APPs were higher in those calves which needed the use of forceful extraction, so we conclude that parturition increases the levels of APPs.

3.2.2 APPs of importance in small ruminants stress and welfare

The number of studies about welfare and APPs in this species of animals is scarce. In ewes, it has been reported that sheep which were transported for 30 and 48 hours, exhibit greater total plasma protein concentrations than those transported for 12 hours. Hp and albumin were considered within the total plasma protein levels (Fisher et al., 2010). More studies should be performed in this topic in order to assess the use of APPs as biomarkers of welfare in sheep and goats.

3.2.3 Porcine APPs of importance in stress and welfare

Pigs belong to the species in which more studies have been carried out regarding animal welfare. In fact, there is a tight European Union Legislation which regulates the conditions of raising animals to assess the well-being.

Condition	Acute Phase Proteins	Reference
Average time transport (24h) + poor transport conditions	↑ Pig-MAP, Hp	Saco et al., 2003 Piñeiro M et al., 2007
Long time transport (48h) + great transport conditions	↑ Pig-MAP	Saco et al., 2003 Piñeiro M et al., 2007
Short time transport (6-12h) + commercial conditions	↑ Pig-MAP, Hp, CRP, SAA ↓ Apo A-I	Saco et al., 2003 Piñeiro M et al., 2007
Long time transport + management and new accommodation	↑ Pig-MAP, Hp, CRP	Salamano et al., 2008
Changes in pattern of food	↑ Pig-MAP, Hp, CRP (males) ↓ Apo A-I (males)	Piñeiro C et al., 2007
Organic versus conventional food	NC Hp	Millet et al., 2005
Housing (gestation crates)	NC Hp, Fb, AGP	Sorrels et al., 2007
Group versus cages	NC Pig-MAP	Rodríguez-Gómez et al., (unpublished data)
Organic versus conventional housing	↑ Hp	Millet et al., 2005
Different stock densities housing	↑ Pig-MAP NC Hp, CRP, Apo A-I	Marco-Ramell et al., 2011

↑ : increased expression; ↓ : decrease expression; NC: no change in expression; Pig-Map: pig-major acute phase protein; Hp: haptoglobin; CRP: C-reactive protein; SAA: serum amyloid A; Apo A-I: apoliprotein A-I; Fb: fibrinogen; AGP: α_1-acid glycoprotein.

Table 9. APPs changes depend on the stressful condition studied.

Different studies have shown that shipment of animals can result in an APP response related to the stress of transportation. Stress in transportation can affect meat quality and as a result, the value of the commercial product (Warris, 1998, 2003). Table 9 summarizes the different studies performed according to the stressful condition studied. In general, APP levels are extremely sensitive to shipment in pigs. Although all major APPs experience changes in their levels, the variation in Pig-MAP and Hp concentrations were constant in the different situations. Apoliprotein A-I (Apo A-I), as a negative APP, was a good biomarker too (Saco et al., 2003; Piñeiro M et al., 2007). APP levels not only were increased after the trip but also as a result of the adaptation to the unfamiliar accommodation, handling procedures and mixing of the animals (Salamano et al., 2008).

The appearance of gastric ulcer is related to stress conditions such as poor management and changes in feeding. This damage leads to huge economical losses in porcine industry. In one study, feeding changes were transient and only in males, possibly due to a higher manifestation of behavior, where the fight, dominance and competition for the food between males are more evident than in females (Piñeiro C et al., 2007). Also, the implementation of organic food did not show any advantage with respect to conventional food (Millet et al., 2005).

Other controversial topic which is in constant study is the type of gestation crates used during gestation in pigs. It is well-known that stress related to gestation can result in weird behaviour to the offspring and disturbances in the immune response leading to higher susceptibility to diseases (Eicher & Burton, 2005). In the majority of the studies performed, no changes were found in APP levels. Only Hp and Pig-MAP proteins altered their concentrations as a result of changes in housing or stock densities housing, respectively. It should be expected that changes between organic versus conventional housing are more patent due to the intention to reproduce natural conditions. However, these results should be interpreted carefully due to some important stressors were not taken into account.

In summary, Pig-MAP and Hp should be considered the best biomarkers of welfare in pig production due to that their analysis can reflect a stressful situation.

4. Disease and acute phase proteins

The discovery of new biomarkers which allow the clinical monitoring of different diseases is nowadays encouraged in order to improve the treatment and therapeutics in each phase of the disease. Therefore, the use of APPs in diagnosis and their application in monitoring of treatments is considered as one of the most interesting applications of these proteins. In this sense, APPs have been widely used in human medicine as biomarkers of inflammation, infection or trauma; however, their use in veterinary medicine is more recent. Thus, a significant progress has been made in the detection, measurement and application of APPs as biomarkers in both companion and farm animals over recent years.

The monitoring of two or more APPs is highly valuable in different diseases as each APP may display a different kinetic after the infection or trauma in the animal (Eckersall, 2000). This information may be of interest to evaluate the progress of the disease and may help in the prognosis of the animal or herd health.

4.1 Disease and APPs in small animals

4.1.1 Disease and APPs in dogs

CRP, SAA, Hp and/or AGP are the main APPs in dogs which may show changes after different infectious diseases, inflammation or other disorders, just as neoplasia (Table 2). For example, an increase of CRP has been observed in parvovirus infection, and in this disease

the magnitude of the increase in APPs could be a useful indicator of the prognosis, being CRP a potent predictor of mortality due to this process (Kocaturk et al., 2010).
High levels of CRP have been related to the onset of sepsis in several disease models in dogs. Thus, the marked increased of CRP reported in dogs infected by canine parvovirus type 2 were due to the appearance of sepsis in these animals (Kocaturk et al., 2010). In fact, the levels reported in this study were similar to those observed previously in dogs with septic processes (Caldin et al., 2009), and deal with the knowledge that usually bacterial infections elicit a much higher APR than viral infections do (Gruys et al., 2005). However, in the previous study (Kocaturk et al., 2010) the use of CRP was evaluated as diagnostic tool for differentiation of survivors versus non survivors displaying a high sensitivity (91%) but a low specificity (61%). For these reasons, the role of CRP as useful marker of sepsis in dogs although indicative of a septic disease remains still controversial.
Serum levels of SAA have been used in the monitoring of responses to treatments as hyperadrenocorticism treatment (Arteaga et al., 2010) or possible complications in postoperative periods as after surgery because of pyometra (Dabrowski et al., 2009). Due to the particular sensitivity of Hp to effects of corticoid in the dog, elevated concentrations of Hp are found after corticosteroids treatments or in cases of hyperadrenocorticism so this protein could be used as a method of screening for canine hyperadrenocorticism but not in monitoring of inflammation because of steroid treatments could interfere with results interpretation (Arteaga et al., 2010; Eckersall & Bell 2010).
In dogs with a fracture or subjected to percutaneous gastrostomy, serum CRP and AGP levels correlated with the condition of the dogs and may be useful in routine testing for inflammation, in preclinical studies and in veterinary clinical biochemistry (Hayashi et al., 2001).
Changes in CRP and Hp have been reported in dogs with lymphatic neoplasia (Mischke et al., 2007). Dogs with mammary neoplasia have high CRP, SAA and Hp levels but the increased concentrations of APPs could be stimulated by different factors, such as metastasis, large size of the primary mass and ulceration or secondary inflammation of the neoplasm (Planellas et al., 2009; Tecles et al., 2009). Serum levels of these APPs are of use in the diagnosis and management of steroid responsive meningitis-arteritis (SRMA), particularly in relation to identifying relapse (Lowrie et al., 2009). Dog with gastric mucosa injury present elevated serum CRP, SAA and Hp levels and may be potentially useful together with gastroscopy in the diagnosis and monitoring of gastric injury (Bayramli & Ulutas, 2008).

4.1.2 Disease and APPs in felines

Feline serum SAA, AGP and/or Hp levels increase in infectious diseases, such as feline infectious peritonitis (FIP), and others inflammatory conditions (Table 3). The serum concentration of SAA may be also a useful marker for evaluating response to treatment and disease exacerbation in feline pancreatitis (Tamamoto et al., 2009).
Elevated concentrations of AGP have been also found in serum of cats with lymphoma although did not provide useful information regarding response or survival of affected animals (Correa et al., 2001).
Increased levels of Hp have been seen in cats affected by FIP (Giordano et al., 2004). In cats experimentally inoculated with feline infectious peritonitis virus Hp levels increased very early and then slight decreased, but two weeks after experimental induction of the disease increased concentrations were found again (Stodddart et al 1988). Besides Hp, increased

levels of AGP have also been reported in cats suffering from FIP, as it has been mentioned above. AGP may trigger several functions related with the regulation of the immune response. In this sense, the sialic acid content has been associated to the defensive functions proposed for AGP, favoring the competition of AGP for cell surface receptors, blocking the binding and the invasion of infectious agents (Ceciliani et al., 2004). Interestingly, it has been postulated that the enhancement in AGP concentrations observed in FIP may play a significant role in the immunopathogenesis of the disease. As stated before, AGP and its glycosylation pattern are associated with resistance or susceptibility to some viral diseases (Rabehi et al 1995). Furthermore, a hyposialylitation of feline AGP has been reported in cats with FIP (Ceciliani et al 2004). Following these results, Paltrinieri et al. (2007c) hypothesized that cats with endemic FCoV infection respond to increased viral burden by increasing the production of AGP and only cats with hyposialylated AGP have persistently increased AGP levels and develop FIP.

4.2 Disease and APPs in large animals

4.2.1 Disease and APPs in equines

The measurement of APPs has potential use in the study of inflammatory disorders in equine medicine (Crisman et al., 2008). Increased serum concentrations of SAA have been found in horses affected by arthritis and a local synthesis of this protein has also been reported in the inflamed joint (Jacobsen et al., 2006a). Synovial fluid SAA concentration seems to be a good marker of infectious arthritis and present advantages as ease and speed of measurement and the fact that concentrations in synovial fluid were not influenced by repeated arthrocentesis in healthy horses (Jacobsen et al., 2006b). High levels of SAA in serum and an increased expression in endometrium have been reported in mares with experimentally induced endometritis (Mette et al., 2010). The serum concentration of SAA has demonstrated its utility for identification of the clinical condition of horses with bacterial pneumonia (Hobo et al., 2007). Horses with enteritis or colitis and conditions characterized by chronic inflammation (e.g. abdominal abscesses, peritonitis, or rectal tears) had SAA concentrations significantly greater than those for horses with other conditions so evaluation of SAA concentrations may be of use in identifying horses with colic attributable to diseases that have inflammation as a primary component of pathogenesis (Vandenplas et al., 2005).

In foals, increased concentrations of SAA have been found in septicaemic animals (Paltrinieri et al., 2008) and has been observed that foals with a strong suspicion of sepsis have significantly higher concentrations of SAA than compromised foals with non-infectious inflammatory disease (Duggan, 2008). The measurement of SAA could be a useful tool in the early diagnosis of neonatal septicaemia (Paltrinieri et al., 2008).

Surgical trauma produces an acute phase response and elective and non-elective surgery induces an increase in the serum levels of SAA (Pollock et al., 2005). The concentration of SAA have shown to reflect the intensity of the surgical trauma and may be useful for comparing surgical trauma associated with novel versus well-established surgical techniques (Jacobsen et al., 2009).

Elevated serum Hp levels have been reported in processes such as experimental aseptic arthritis, experimental local aseptic inflammation, experimentally induced noninfectious laminitis, grass sickness (equine dysautonomia) or castration (Petersen et al., 2004) (Table 4).

4.2.2 Disease and APPs in cattle

In ruminants, the acute phase response is different from other species since Hp is considered as a major APP (Eckersall & Bell 2010). Hp serum levels have been found increased in several inflammatory diseases such as endometritis, pneumonia, enteritis, peritonitis, mastitis and endocarditis (Murata et al., 2004; Petersen et al., 2004) (Table 5). In the case of metritis Hp values may assist in the early detection of the disease, providing increased opportunities for early treatment and prevention (Huzzey et al., 2009). Lameness due to claw disorders can be associated with a systemic acute phase response and elevated serum Hp in dairy cattle and the values of this protein can be used for monitoring the effectiveness of different treatments (Smith et al., 2010). In lame cows as a result of hoof disease increased concentrations of serum SAA were found while Hp values did not increased significantly what could mean that a greater stimulation associated with inflammation is needed for serum haptoglobin to increase (Kujala et al., 2010).

The serum values of SAA seem to be more sensitive marker for acute inflammation than Hp values (Horadagoda et al., 1999). In calves with chronic respiratory diseases elevated concentrations of Hp and SAA were found, and were significantly higher in dead or euthanized calves compared with calves in improved health status during therapy, so their evaluation could be useful in the determination of prognosis of the respiratory disease (Tóthová et al., 2010). In the case of viral pneumonias, the concentration of both proteins are elevated but the magnitude and duration of the Hp response was found to correlate well with the severity of clinical signs (fever) and with the extent of lung consolidation while SAA responded most rapidly to infection, so this last protein seems to be a more sensitive marker for viral pneumonia (Heegaard et al., 2000). In experimental infection with *Mannheimia haemolytica*, SAA was found to be more rapidly induced than Hp (Horadagoda et al.,1994), but in field cases, Hp produce a bigger and more prolonged response giving rise to its higher sensitivity in detecting disease (Angen et al., 2009).

The serum concentrations of Hp and SAA are increased in cases of mastitis (Gerardi et al., 2009; Petersen et al., 2004; Safi et al., 2009). In animals suffering from this disorder, the levels of these proteins have been also measured in milk. Hp levels in milk in cows affected by clinical mastitis were higher in cows with moderate to severe versus mild systemic disease (Wenz et al., 2010). In a study carried out by Safi et al. (2009) in Holstein cows from 7 different dairy farms the levels of Hp and amyloid A were measured in milk (AAM) and serum in order to evaluate the use and compare the accuracy of both APPs in these specimens for the diagnosis of subclinical mastitis based on bacterial culture results and with comparison with the California mastitis test (CMT) and somatic cell counts (SCC). The results of the study showed that the bacteria most found in the cases of subclinical mastitis were *Streptococcus agalactiae* and *Staphylococcus aureus* and the most accurate test for the diagnosis was AAM followed by CMT, SCC, HP in milk, SAA in serum and Hp in serum. Therefore test on milk generally were more accurate than test in serum in the diagnosis of subclinical mastitis. In another study carried out by Gerardi et al. (2009) about the use of SAA and AAM for the diagnosis of subclinical mastitis, the levels of AAM measured with a milk ELISA kit were significantly different between cows with subclinical and clinical mastitis and resulted to be a better tool for distinguishing subclinical from clinical mastitis than AAM measured with a serum ELISA kit. The results of this study also showed that the measurement of AAM could allow the identification of subclinical mastitis in equal or higher measure than SCC so the control of AAM and SAA on dairy farms could reduce both the laboratory costs and the time required for milk analysis.

Serum levels of Hp and SAA have been measured in cows with left displaced abomasum, right displaced abomasum or abomasal volvulus and the values were most strongly associated with liver fat percentage than with the alteration in abomasums so an increase in SAA or Hp may indicate the presence of hepatic lipidosis in cattle with abomasal displacement (Guzelbektes et al., 2010)
AGP is considered as moderate APP in cow. Elevated serum levels of this protein have been reported in cows with respiratory disease (Nikunen et al., 2007). In experimental infections with *Pasteurella multocida* increases in the concentrations of AGP have been found to be more gradual and to remain elevated for longer than those observed for SAA or Hp (Dowling et al., 2002). Elevated serum levels of AGP have been also reported in animals with mastitis (Eckersall et al., 2001).
CRP serum levels have shown their utility as a marker or tool for evaluating the health status of a herd and could also be considered as useful criteria to assess the stress levels as well as in early surveillance of disease conditions in a dairy herd (Lee et al., 2003).
Another utility of APPs could be the assessment of animal health and welfare as an aid to meat inspections (Eckersall & Bell, 2010). Hp and SAA serum concentrations al slaughter have been found increased in cows with infectious and metabolic diseases compared to animal with minor lesions and animal with acute lesions compared with healthy animals (Hirvonen et al., 1997; Tourlomousis et al., 2004).

4.2.3 Disease and APPs in small ruminants

In goats, Hp and SAA can be considered as major APPs, while ASG and Fb can be considered as moderate (Table 1). Increase in Hp, SAA, ASG, and Fb serum concentrations have been found after inducing an inflammatory response by subcutaneous injection of turpentine oil (González et al., 2008). Elevated serum levels of Hp have been reported in experimentally induced pregnancy toxemia in goats (González et al., 2011) (Table 6).
In sheep, serum Hp seems to be useful as a marker for the presence of bacterial infection (Skinner & Roberts, 1994). Serum Hp, SAA and AGP were increased in an experimental model of caseous lymphadenitis, suggesting the results that AGP could have a role as a marker for chronic conditions in sheep (Eckersall et al., 2007). Increased serum CRP, Hp, Cp and Fb levels have been reported in animals infected with *M. haemolytica* (Ulutas & Ozpinar, 2006) (Table 6).

4.2.4 Disease and APPs in swine

Increased serum levels of APPs have been reported in pigs experimentally and naturally infected with different virus and bacteria. Hp, CRP, SAA and Pig-MAP increased serum levels have been recently reported in pigs experimentally infected with porcine reproductive and respiratory syndrome virus (PRRSV) by our research group (Gómez-Laguna et al., 2010b). In this study we found an increase at 10 days post inoculation (dpi) in the serum levels of Hp and Pig-MAP. The serum levels of CRP and SAA showed a delayed increase at 17 dpi, being this last APP which reached the highest increase. The increase in the serum concentrations of Hp coincided with the highest titer of viraemia and a light enhancement in the levels of IL-6 and TNF-α, and might be related with and increased expression of IL-10. CRP participates in the complement activation and opsonization, and induces cytokine production by macrophages, whereas SAA is chemotactic for monocytes, T cells and polymorphonuclear, so the delayed increased expression found in both APPs may contribute to the establishment of an impaired non-efficient host-immune response. The result of our study suggested a modulation of the immune response by the enhanced expression of Hp, and the poor or/and delayed expression of TNF-α, CRP and SAA making feasible a prolonged viraemia and an inefficient PRRSV clearance. Another study carried out by our research group showed that the values of Hp and CRP in saliva and meat juice showed a similar kinetic than in serum in PRRSV-infected animals, so these samples could serve as complementary or alternative biomarkers in this disease (Gómez-Laguna et al., 2010a). The serum levels of these proteins are also increased in swine influenza virus (SIV) experimentally infected animals (Barbé et al., 2011). In pigs experimentally infected with classical swine fever and African swine fever viruses the serum concentrations of Hp, CRP and SAA were increased, being the levels of this last protein what more increase presented in the animals infected by both viruses (Sánchez-Cordón et al., 2007).

In animals naturally infected by PRRSV serum levels of Hp, CRP and SAA were found increased but not Pig-MAP concentrations. This APPs did not present any change when compared with Specific Pathogen Free (SPF) pigs taken as controls. In animals affected with Aujeszky's disease virus (ADV) only Hp showed increased levels, whereas pigs with porcine circovirus type 2 (PCV2) showed marked modifications in all APPs tested. The increases in the concentrations of APPs were higher in animals with clinical signs and concurrent bacterial processes (Parra et al., 2006). In a study in farms with animals clinically affected by Postweaning Multisystemic Wasting Syndrome (PMWS) caused by PCV2, the serum levels of Hp and Pig-MAP correlate with PCV2 viremia and the clinical course of the disease, concluding that Pig-MAP, in the conditions of this study, was better indicator of the PMWS status than Hp (Grau-Roma et al., 2009). In another study in farms affected by PMWS the increase in the viral load did not induce any SAA response (Wallgren et al., 2009).

In pigs experimentally infected by *Streptococcus suis* showed increased serum concentrations of Hp, CRP, SAA and Pig-MAP (Sorensen et al., 2006). In an experimental infection with *Actinobacillus pleuropneumoniae* increased serum levels of CRP and SAA were found but extrahepatic expression of these two proteins and of Hp and Pig-MAP was also detected in peripheral lymphoid tissues by PCR (Skovgaard et al., 2009). Extrahepatic presence of Hp has been also detected in lung by immunohistochemistry (Hiss et al., 2008). In field cases of enzootic pneumonia (EP) caused by *Mycoplasma hyopneumoniae* elevated serum levels of Hp, CRP, SAA and Pig-MAP have been reported (Parra et al., 2006) (Table 7).

In slaughter-aged pigs, the serum levels of Pig-MAP resulted to be more sensitive marker than Hp to differentiate animals suffering of pleuritis and cranio-ventral pulmonary consolidations (Saco et al., 2010). In a study carried out at slaughter by our research group serum levels of Hp and CRP in apparently healthy pigs were significantly higher in animals with lesions than those without lesions. In this same study was found that the extent and severity of lung lesions were related to serum levels of Hp (Pallarés et al., 2008). In another study the findings indicative of lesions compatible with enzootic pneumonia were associated with increased serum Hp at slaughter (Amory et al., 2004). In pigs with carcass condemnations due to abscesses increased serum APPs have been also reported (Heinonen et al., 2010). The use of APPs in finishing pigs just before sacrifice could provide information to the veterinary inspector about the possible appearance of lesions in these pigs and could serve as a tool to the meat industry to differentiate pigs with different health status that probably will match with different quality of carcasses (Pallarés et al., 2008).

5. Conclusion: APP in the evaluation of prophylaxis and therapeutic strategies

APPs may act as biomarkers of inflammation allowing us to study the progression of the inflammatory response which is evoked during the acute phase of several diseases. The application of different therapeutic agents should diminish the intensity and the length of the inflammation and, therefore, the APR. Monitoring diseases and their treatments by means of APPs, may allow us to determine the efficiency and efficacy of a specific treatment. In this sense, Arteaga et al. (2010) monitored the response of canine hyperadrenocorticism to trilostane, and concluded that whereas only Hp (together with cholesterol and alkaline phosphatase) give some information about the control of the disease, no information was obtained from SAA or CRP, despite the former also decreased after the treatment. On the other hand, CRP represents an interesting parameter to measure in other processes, just as in canine lymphoma, where a significant decrease in CRP values was associated to remission after treatment with specific cytotoxic drugs (Nielsen et al., 2007). Specific APPs have been reported as value tools in monitoring both infectious diseases, just as CRP and Cp (but not SAA or Hp) in leishmaniasis (Martínez-Subiela et al., 2003) or CRP (but not Hp) in trypanosomiasis (N'dungu et al., 1991), and inflammatory processes, just as SAA in feline acute pancreatitis (associated with remission and recurrence) (Tamamoto et al., 2009) or Hp in bovine respiratory disease (Carter et al., 2002). In other conditions, just as canine hemolytic anemia, the changes in APPs were not useful to monitor the success of specific treatments (Griebsch et al., 2009; Mitchell et al., 2009).

On the other side, some prophylactic strategies are carried out in order to prevent the disease. One of the most common prophylactic strategies is the use of vaccines, which may prepare the organism to fight against a specific pathogen. Some vaccines are made with peptidic fragments from the microorganism or with the whole microorganism inactivated by different methods. Thus, vaccines may develop also an APR which may have an adverse effect and limit the efficacy and safety of these prophylactic strategies (Gruys et al., 2005). For these reasons, APPs may be used to determine the usefulness of vaccines as prophylactic agents, determining the magnitude of the inflammatory response evoked by their use. Moreover, aminoacids are required for the production of APPs, specifically phenylalanine, tryptophan and tyrosine may be detected in high percentage in some positive APPs. Therefore, vaccination may limit in some cases the recovery of the diseased animal acting opposite to the anabolism of the muscle (Gruys et al., 2005).

The inflammatory and the acute phase responses have been measured in cattle vaccinated with different clostridial vaccine candidates, being observed a higher expression of Hp and a decrease in feed consumption when a multiple clostridial- instead of a mono-clostridial vaccine was used, which points to the potential negative effects of multiple clostridial-vaccinations (Stokka et al., 1994). Moreover, the utility of Hp values have been shown in the follow-up of the trimming and antibiotic treatment against several claw disorders (Smith et al., 2000).

In pigs, monitoring the APPs has been widely used to determine the usefulness of specific vaccines against both bacteria and viruses. A panel of APPs (Pig-MAP, Hp, CRP and Apo A-I) has been used in order to monitor pigs challenge against both the bacteria *Hameophilus parasuis* and commercial and non-commercial bacterins finding a lower expression of APPs in vaccinated animals together with a shorter course of the disease and higher survival rates (Martín de la Fuente et al., 2010). Apo A-I and Pig-Map has been shown to be useful tools to monitor vaccination against Aujeszky's disease, showing the vaccinated animals none or only mild clinical signs, a less pronounced APR and recovered earlier to normal values (Carpintero et al., 2007). Nonetheless, further studies are required in order to assess the predictive value of APPs in vaccine testing.

Although a wide range of studies have been carried out to determine the role of APPs in several conditions just as stress, inflammation, infection or vaccination there is still necessity for establishing reference values which allow interpreting the results from the different studies and disorders. Some of this information may be available for some species of domestic animal; however, there is no still a global consensus to accept specific ranges for each APP in each species, as well as, validation of specific analytical techniques which enable the interlaboratory comparison of results.

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7. References

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